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Subtle Post-Procedural Cognitive Dysfunction After Atrial Fibrillation Ablation

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Objectives This study sought to determine whether post-operative neurocognitive dysfunction (POCD) occurs after ablation for atrial fibrillation (AF).

Background Ablation for AF is a highly effective strategy; however, the risk of transient ischemic attack and stroke is approximately 0.5% to 1%. In addition, magnetic resonance imaging studies report a 7% to 14% prevalence of silent cerebral infarction. Whether cerebral ischemia results in POCD after ablation for AF is not well established.

Methods The study included 150 patients; 60 patients undergoing ablation for paroxysmal atrial fibrillation (PAF), 30 patients undergoing ablation for persistent atrial fibrillation (PeAF), and 30 patients undergoing ablation for supraventricular tachycardia (SVT) were compared with a matched nonoperative control group of patients with AF awaiting radiofrequency ablation (n = 30). Eight neuropsychological tests were administered at baseline and at 2 days and 90 days post-operatively. The tests were administered at the same time points to the nonoperative control group. The reliable change index was used to calculate POCD.

Results The prevalences of POCD at day 2 post-procedure were 28% in patients with PAF, 27% in patients with PeAF, 13% in patients with SVT, and 0% in control patients with AF ($p = 0.007$). At day 90, the prevalences of POCD were 13% in patients with PAF, 20% in patients with PeAF, 3% in patients with SVT, and 0% in control patients with AF ($p = 0.03$). When analyzing the 3 procedural groups together, 29 of 120 patients (24%) manifested POCD at day 2 and 15 of 120 patients (13%) at day 90 post-procedure ($p = 0.029$). On univariate analysis, increasing left atrial access time was associated with POCD at day 2 ($p = 0.04$) and day 90 ($p = 0.03$).

Conclusions Ablation for AF is associated with a 13% to 20% prevalence of POCD in patients with AF at long-term follow-up. These results were seen in a patient population with predominant $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack) scores of 0 to 1, representing the majority of patients undergoing ablation for AF. The long-term implications of these subtle changes require further study. (J Am Coll Cardiol 2013;62:531–9) © 2013 by the American College of Cardiology Foundation

Ablation for atrial fibrillation (AF) is a highly effective strategy for the management of this common arrhythmia. However, the procedure has a risk of major complications, including a 0.5% to 1% risk of transient ischemic attack or stroke (1). Prolonged placement of left atrial catheters and atrial endocardial damage caused by ablation may trigger thrombus formation despite use of anticoagulation. Recent magnetic resonance imaging (MRI) studies have demonstrated the development of new cerebral lesions after irrigated AF ablation in 7% to 14% of apparently asymptomatic patients (2,3). Whether subtle neurocognitive dysfunction may occur after AF ablation procedures has not been well established.

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We evaluated the prevalence of post-operative cognitive dysfunction (POCD) in patients after radiofrequency ablation (RFA) for AF and compared this with a nonprocedural control population of age-matched patients with AF. We also studied a group of matched patients with supraventricular

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Abbreviations and Acronyms

ACT = activated clotting time

AF = atrial fibrillation

CERAD = Consortium to Establish a Registry for Alzheimer's Disease

$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack

CI = confidence interval

IQ = intelligence quotient

MRI = magnetic resonance imaging

OR = odds ratio

PAF = paroxysmal atrial fibrillation

PeAF = persistent atrial fibrillation

POCD = post-operative cognitive dysfunction

RCI = reliable change index

RFA = radiofrequency ablation

SVT = supraventricular tachycardia

tachycardia (SVT) undergoing ablation as a comparison group.

Methods

Patient selection. The study included a total of 150 patients in 4 groups: 1) 60 patients with paroxysmal AF (PAF) undergoing RFA for drug-refractory AF; 2) 30 patients with persistent AF (PeAF) undergoing RFA for drug-refractory AF; 3) 30 patients with SVT undergoing RFA; and 4) 30 patients with AF awaiting RFA for symptomatic drug-refractory AF (control group). These patients were studied during the waiting period before scheduled ablation. They were of similar age and met the inclusion and exclusion criteria described in the following text.

Consecutive patients presenting for RFA of AF were approached for inclusion into the study. Patients with a history suggestive of, or who had, documented SVT and who were of a similar age group (age 40 to 70 years) were also recruited. This group was included as an age-matched population of patients undergoing an ablation procedure to control the effect of general anesthesia on outcomes. Patients were not specifically selected based on the presumed location of tachycardia (i.e., left or right sided). The protocol was approved by the Melbourne Health Research and Ethics Committee, and written informed consent was obtained from all patients. Exclusion criteria included pre-existing neurological or clinically evident neurovascular disease, significant pre-morbid depression and/or anxiety, anticipated difficulty with neurocognitive assessment (e.g., deafness, language difficulties), and geographic remoteness.

Ablation procedures. For patients with PAF, the ablation strategy consisted of wide encirclement of the pulmonary vein antra without additional adjunctive ablation (4,5). The endpoint was demonstration of pulmonary vein entrance and exit block. Patients with PeAF had adjunctive ablation at the discretion of the treating electrophysiologist.

In patients receiving anticoagulation therapy before pulmonary vein antral isolation, warfarin was stopped 5 days before the procedure and treatment with full-dose low-molecular-weight heparin was commenced. Transesophageal echocardiography was performed in all patients immediately before the procedure to rule out atrial or atrial appendage thrombus. A decapolar catheter was positioned in the coronary sinus and a quadripolar catheter in the His bundle position. Two 8.5-F-long sheaths (SL1, St. Jude Medical, Minneapolis, Minnesota) were introduced into the left atrium with trans-septal puncture performed under fluoroscopic and transesophageal echocardiography guidance. A Lasso circular mapping catheter (Biosense Webster, Foster City, California) or a Reflexion spiral catheter (St. Jude Medical) was introduced through the SL1 sheath into the left atrium for electrical mapping of the pulmonary veins. An irrigated ablation catheter (4 mm, D curve, Navistar Thermocool, Biosense Webster) was introduced through the SL1 sheath into the left atrium for ablation (maximum power: 30 to 35 W). Patients were treated with intravenous heparin to maintain an activated clotting time (ACT) of 300 to 350 s throughout the procedure. For each patient, an ACT was recorded that represented the mean of all ACTs obtained throughout the procedure.

After ablation, treatment with warfarin was initiated and enoxaparin was administered at a full dose (1 mg/kg twice daily) starting 6 h after the procedure. Enoxaparin was continued until a therapeutic international normalized ratio (2.0 to 3.0) was attained. Warfarin was administered for at least 90 days or indefinitely in patients with a $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack) score ≥2 (1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points for prior stroke or thromboembolism). Antiarrhythmic therapy was continued unchanged for 90 days after the procedure during the study period. No new antiarrhythmic therapy was initiated in the post-operative period, and drug therapy remained constant for the duration of the protocol.

Patients with SVT underwent RFA targeted at the specific underlying arrhythmia. In patients with SVT and an arrhythmia focus originating from the left atrium requiring trans-septal access, a single trans-septal puncture was performed, followed by a bolus of 5,000 U heparin. Thereafter, patients were treated with intravenous heparin to maintain an ACT of 200 to 250 s throughout the procedure. Patients with a right-sided SVT mechanism were treated with a baseline of 2,000 U heparin only.

Anesthesia. All patients with AF and SVT underwent RFA while under general anesthesia. Patients were given induction anesthesia with a combination of propofol, midazolam, and fentanyl. General anesthesia was maintained throughout the procedure using volatile anesthetic agents (sevoflurane or desflurane). Routine measures of oxygenation and temperature monitoring were documented. Bispectral Index monitors (BIS, Covidien, Boulder, Colorado) were used to estimate the depth of anesthesia throughout the procedure. Arterial blood gas measurements were taken at random intervals throughout the procedure to measure intraprocedural factors such as pH, glucose level, and lactate level that may potentially modify assessments of POCD.

POCD and neuropsychological testing. Neuropsychological testing comprised 8 tests, based on the Canadian Study of Health and Aging, administered to all patients by a trained interviewer (6–10). The results are given as the

number of correct answers or the time taken to complete the test. Testing was administered at 3 time points:

1. Baseline tests were administered within 7 days before the procedure.
2. Post-procedure tests were administered 24 to 48 h post-procedure.
3. Late post-procedure tests were administered 90 days post-procedure.

The individual tests consisted of 8 auditory and written tests, described in Table 1 (8). These tests included the following:

1. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Auditory Verbal Learning Test (Immediate and Delayed)
2. Trail Making Task Part A
3. Trail Making Task Part B
4. Digit Symbol Substitution Test
5. Controlled Oral Word Association Test
6. CERAD Semantic Fluency Test
7. Grooved Pegboard Test (Dominant Hand)
8. Grooved Pegboard Test (Nondominant Hand)

Absolute test scores were reversed for timed tasks (Trail Making Task Part A and B, Grooved Pegboard Test Dominant and Nondominant Hands), so a decrease in test score reflected cognitive decline for all tests (8–10).

In addition to the neuropsychological tests, patients were also administered the following tests:

1. The Mini-Mental State Examination was administered to exclude pre-existing cognitive impairment at baseline.
2. The National Adult Reading Test was administered to estimate baseline intelligence quotient (IQ).
3. Visual analog scales were administered to assess the presence of mood disorder and fatigue levels that may affect the diagnosis of POCD. Patients were asked to mark a line standardized to 10 cm in length to estimate their current levels of anxiety, depression, and fatigue (8).

Test scores were analyzed to identify POCD using the reliable change index (RCI). The RCI rule was applied as described by Rasmussen et al. (10,11) and was calculated by subtracting the preoperative score (X_1) from the postoperative score (X_2), giving Δ_x for each individual patient for each neuropsychological test. The RCI was similarly calculated for the control group, and the mean expected change for the controls, Δ_{xc}, was then subtracted from the patient's score, thereby eliminating any learning and practice effect. This score was then divided by the SD for the change in test results of the control group, SD(Δ_{xc}), controlling for the expected variability. These scores were then used to create

Table 1 Description of Neuropsychological Tests*

Test	Description	Cognitive Domain
CERAD Auditory Verbal Learning Test-Immediate	Patients are read a list of 10 words and are asked to recall as many words as possible. The maximum number of correct words recalled is documented. This is repeated a further 2 times; however, the word order is changed each time. The results of each individual trial are taken as the scores for this test.	Memory
CERAD Auditory Verbal Learning Test-Delayed	After a 15-min delay after completion of the CERAD Auditory Verbal Learning Test-Immediate, patients are asked to recall as many of the 10 words as possible without further prompting or re-reading of the list. The maximum number of correct words remembered is taken as the score.	Memory
Trail Making Task Part A	Consists of 25 circles distributed over a sheet of paper numbered 1–25. The patient is instructed to draw lines to connect the numbers in ascending order as quickly as possible. The time taken to complete the task is taken as the score.	Executive functioning
Trail Making Task Part B	Consists of 25 circles distributed over a sheet of paper; the circles include both numbers (1–13) and letters (A–L). The patient is instructed to draw lines to connect the circles in an ascending pattern but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, and so on). The time taken to complete the task is taken as the score.	Executive functioning
Digit Symbol Substitution Test	Requires patients to reproduce on paper, within 90 s, as many coded symbols as possible within blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with symbols. The number of correct symbols reproduced in 90 s is taken as the score.	Memory and processing function
Controlled Oral Word Association Test	Patients are instructed to say as many words as possible starting with a given letter within 60 seconds. F, A, and S are tested.	Verbal fluency test, measuring frontal and temporal lobe function
CERAD Semantic Fluency Test	Patients are instructed to generate a list of as many words as possible from a predefined category (animals) within 60 seconds. The number of correct answers is taken.	Verbal fluency test of semantic memory, measuring temporal and frontal lobe function
Grooved Pegboard Test (Dominant Hand)	Requires patients to insert 25 keyed pegs into a specially designed pegboard with randomly positioned slots. Pegs must be rotated to match the hole before they can be inserted. The duration taken to complete the task in seconds is taken.	Requires complex visual-motor coordination and evaluates lateralized injury
Grooved Pegboard Test (Nondominant Hand)	Requires patients to insert 25 keyed pegs into a specially designed pegboard with randomly positioned slots. Pegs must be rotated to match the hole before they can be inserted. The duration taken to complete the task in seconds is taken.	Requires complex visual-motor coordination and evaluates lateralized injury

*Adapted from Silbert et al. (8).
CERAD = The Consortium to Establish a Registry for Alzheimer's Disease.

a combined test score ($\Sigma Z_{combined}$) using the sum of z-scores for each test ($\Sigma Z_{a,b,c,d,etc.}$) divided by the SD of this summation in the control group (SD[$\Sigma Z_{control}$]). POCD was defined in an individual when the RCI score was less than −1.96 on ≥2 tests and/or the combined z-score was less than −1.96. This classifies POCD on the basis of a significant failure on ≥2 tests or a more generalized subtle decline across the 8 neuropsychological tests (10,11).

This evaluation identifies any change in performance over time compared with baseline performance. As described in the preceding text, POCD was considered present with either a severe deterioration in a few tests or a less severe deterioration in many tests relative to baseline functioning. The presence or absence of deficits in control patients with AF over time (day 2 and day 90) was also assessed to verify the performance of the control population.

Statistical analysis. Group comparisons were made using unpaired Student t tests or one-way analysis of variance for continuous variables, the Kruskal-Wallis test for ranked data, and chi-square test for dichotomous variables. The type I error rate was controlled using the Holm-Bonferroni step-down procedure for multiple comparisons (12). Associations were determined using univariable analysis. A probability value of <0.05 indicated statistical significance.

Results

Baseline characteristics. The baseline and clinical characteristics of the patients with PAF, patients with PeAF, patients with SVT, and the control population are shown in Table 2. The mean age was similar across the 4 groups. There was a higher proportion of men with AF (81%) compared with SVT (43%). Other baseline characteristics, including $CHADS_2$ risk factors, were comparable between the groups. Baseline medications are also shown in Table 2. A higher proportion of patients with PAF were treated with aspirin and a higher proportion of patients with PeAF were treated with warfarin before the ablation procedure. Use of antiarrhythmic drugs and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers was higher in patients with PAF. The proportions of patients treated with beta-blockers were not significantly different between the 4 groups.

Procedural characteristics. Successful pulmonary vein isolation was achieved in 59 of 60 patients (98%) with PAF and 29 of 30 patients with PeAF (97%) (p = 1.0). Ten of 30 patients (33%) with PeAF underwent adjuvant linear ablation, including 2 of 10 patients who also underwent adjuvant ablation of complex fractionated electrograms. Of the patients with SVT, atrioventricular node re-entrant tachycardia was present in 14 patients, atrioventricular re-entrant tachycardia in 7 patients, and atrial tachycardia in 5 patients; in addition, multiple tachycardia mechanisms were present in 4 patients (2 patients with atrioventricular node re-entrant tachycardia and atrial tachycardia, 1 patient with atrioventricular re-entrant tachycardia and atrial tachycardia, and 1 patient with multiple atrioventricular re-entrant tachycardia pathways). Of these patients, 7 required trans-septal access for ablation of left-sided tachycardia and the remaining 23 required right-sided access only.

A comparison of procedural parameters is shown in Table 3. There was no difference between patients with PAF, PeAF, and SVT when comparing depth of anesthesia (as measured by Bispectral Index score), mean systolic blood

Table 2 Baseline and Clinical Characteristics

	Paroxysmal Atrial Fibrillation (n = 60)	Persistent Atrial Fibrillation (n = 30)	Supraventricular Tachycardia (n = 30)	Control (n = 30)	p Value
Age (yrs)	57 ± 9	53 ± 10	56 ± 11	53 ± 9	NS
Male	45 (75)	28 (93)	13 (43)	23 (77)	0.0002
Duration of symptoms (months)	84 ± 72	81 ± 75	92 ± 180	78 ± 62	NS
Left ventricular ejection fraction (%)	59 ± 8	55 ± 8	59 ± 5	59 ± 5	NS
Hypertension	31 (52)	10 (33)	8 (27)	10 (33)	NS
Diabetes mellitus	5 (8)	1 (3)	3 (10)	1 (3)	NS
Coronary artery disease	6 (10)	1 (3)	2 (7)	0 (0)	NS
Previous transient ischemic attack	2 (3)	1 (3)	0 (0)	1 (3)	NS
Hypercholesterolemia	13 (22)	8 (27)	6 (20)	2 (7)	NS
Smoker/ex-smoker	13 (22)	4 (13)	4 (13)	3 (10)	NS
$CHADS_2$ score	0.75 ± 0.8	0.70 ± 0.9	0.67 ± 0.7	0.60 ± 0.8	NS
Angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker	22 (37)	6 (20)	6 (20)	7 (23)	0.03
Calcium channel blocker	13 (22)	6 (20)	4 (13)	6 (20)	NS
Beta-blocker	10 (17)	8 (27)	8 (27)	7 (23)	NS
Antiarrhythmic drug (including sotalol)	43 (72)	13 (43)	12 (40)	15 (50)	0.01
Warfarin	22 (37)	22 (73)	1 (3)	9 (30)	<0.0001
Aspirin	32 (53)	5 (17)	5 (17)	10 (33)	0.0002

Values are mean ± SD or n (%).
$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack.

Table 3 Procedural Characteristics

	Paroxysmal Atrial Fibrillation (n = 60)	Persistent Atrial Fibrillation (n = 30)	Supraventricular Tachycardia (n = 30)	p Value (Analysis of Variance)
Left atrial access time (min)	159 ± 35	166 ± 42	92 ± 45*	0.0007
Radiofrequency duration (min)	50 ± 19	47 ± 20	9 ± 10	<0.0001
Fluoroscopy time (min)	41 ± 10	44 ± 13	20 ± 13	<0.0001
Activated clotting time (s)	312 ± 31	311 ± 20	170 ± 32	<0.0001
Bispectral index score	42 ± 6	38 ± 8	43 ± 5	NS
Systolic blood pressure	110 ± 8	111 ± 7	115 ± 10	NS
pH	7.4 ± 0.1	7.3 ± 0.1	7.4 ± 0.1	NS
Glucose	6.2 ± 1.0	6.4 ± 0.9	6.7 ± 1.4	NS
Direct current cardioversion	0 (0)	1 (2)	0 (0)	<0.0001

Values are mean ± SD or n (%). *Patients with left-sided tachycardia.

pressure, and intraprocedural pH and glucose levels. The periprocedural ACT was significantly greater in patients undergoing ablation for AF, but not between patients with PAF and PeAF. Compared with patients with SVT who had left-sided tachycardia, patients with PAF and PeAF had significantly longer left atrial access time, radiofrequency time, and fluoroscopy time. There was no significant difference between these parameters in patients with PAF compared with PeAF ($p = 0.5$, $p = 0.3$, and $p = 0.2$ for left atrial access time, radiofrequency time, and fluoroscopy time, respectively). A significantly higher proportion of patients with PeAF underwent cardioversions during the procedure than did patients with PAF or SVT (PeAF: 1 [2%]; PAF: 0 [0%]; SVT: 0 [0%]; $p < 0.0001$).

No patient developed a stroke/transient ischemic attack, or other clinical embolic phenomenon post-procedure.

Clinical outcomes. BASELINE DEMOGRAPHICS AND PATIENT CHARACTERISTICS. The scores for anxiety, depression, and fatigue are presented in Figures 1 to 3. There were no differences in anxiety levels between the 4 groups at the 3 time points assessed. In the assessment of depression, patients with PeAF had an increased score at the day-2 testing time point only. Patients with PeAF rated their levels of fatigue higher than did the other 3 study populations at baseline and day 90. The estimated IQ as measured by the National Adult Reading Test was not clinically different between the 4 groups (PAF: 115 ± 10; PeAF: 119 ± 9; SVT: 115 ± 12; control: 121 ± 7).

Neuropsychological test outcomes. IMMEDIATE (DAY 2 POST-OPERATIVE) NEUROPSYCHOLOGICAL TEST RESULTS. Testing was performed between 24 and 48 h after RFA in patients with AF and SVT (mean: 36 ± 10 h) and between 24 and 48 h after baseline testing in the AF control population (mean: 39 ± 18 h). POCD occurred in 17 of 60 patients with PAF (28%; 95% confidence interval [CI]: 18% to 41%), 8 of 30 patients with PeAF (27%; 95% CI: 13% to 44%), and

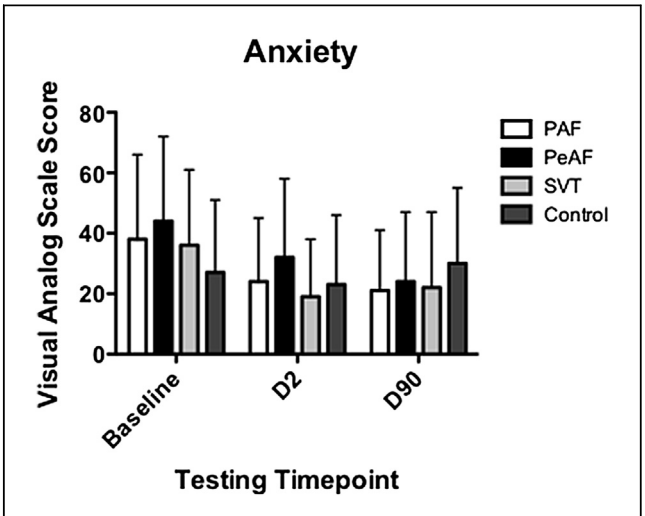

Figure 1 Visual Analog Scale Scores for Anxiety at Baseline, D2, and D90

There was no difference in reported anxiety levels between the patient groups. All p = NS. D = day; PAF = paroxysmal atrial fibrillation; PeAF = persistent atrial fibrillation; SVT = supraventricular tachycardia.

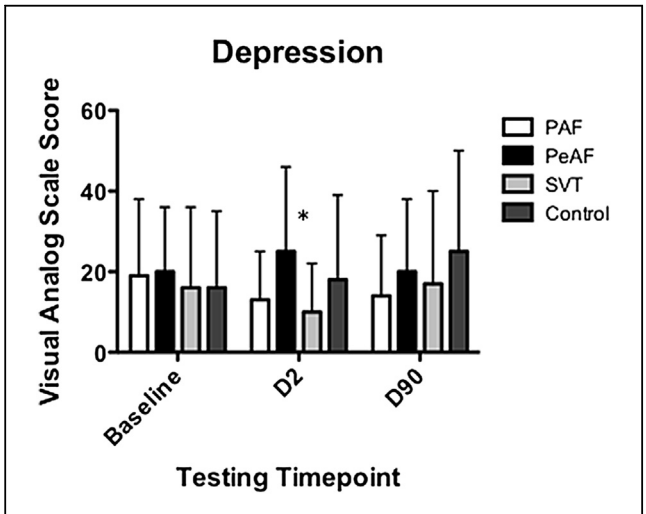

Figure 2 Visual Analog Scale Scores for Depression at Baseline, D2, and D90

Patients with PeAF reported higher levels of depression at day 2 only. There was no other difference in reported levels of depression between the patient groups. *D2, p = 0.01; other, p = NS. Abbreviations as in Figure 1.

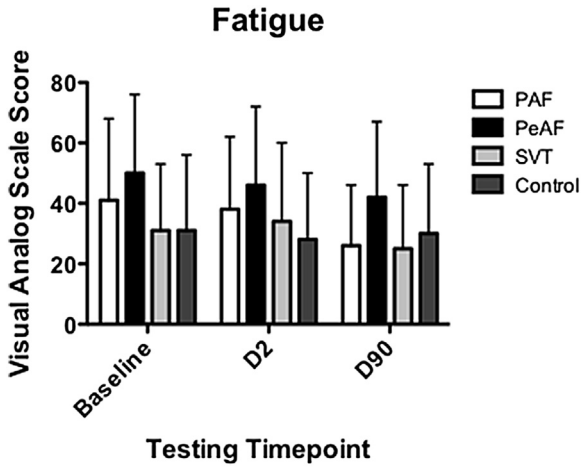

Figure 3 Visual Analog Scale Scores for Fatigue at Baseline, D2, and D90

Patients with persistent atrial fibrillation reported higher levels of fatigue at baseline and day 90. $p < 0.01$ Baseline and D90; D2, $p = NS$. Abbreviations as in Figure 1.

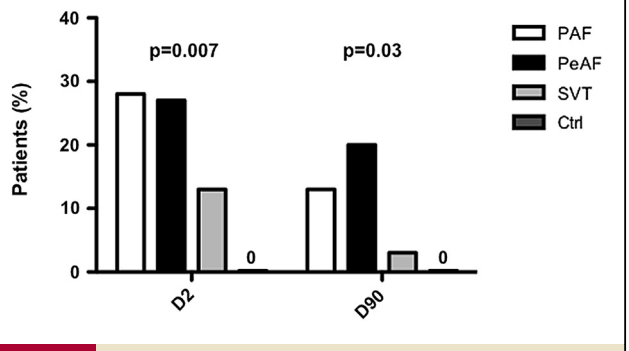

Figure 4 Prevalence of POCD Post-Ablation for AF

At day 90, the prevalence of POCD in patients with PAF was 13% and in patients with PeAF was 20%. POCD = post-operative cognitive dysfunction; other abbreviations as in Figure 1.

4 of 30 patients with SVT (13%; 95% CI: 4% to 29%). No control patient deteriorated at this time compared with baseline to qualify for classification of POCD ($p = 0.007$) (Fig. 4).

LONG-TERM (DAY 90 POST-OPERATIVE) NEUROPSYCHOLOGICAL TEST RESULTS. At 90 days, POCD occurred in 8 of 60 patients with PAF (13%; 95% CI: 6% to 24%), 6 of 30 patients with PeAF (20%; 95% CI: 9% to 37%), 1 of 30 patients with SVT (3%; 95% CI: 0.2% to 15%), and 0 of 30 control patients with AF ($p = 0.03$) (Fig. 4).

There was no significant difference in the prevalence of POCD between the PAF and PeAF groups. When analyzing the 3 procedural groups together, 29 of 120 patients manifested POCD at day 2 (24%; 95% CI: 16% to 32%) and 15 of 120 at day 90 post-ablation procedure (13%; 95% CI: 7% to 19%).

When comparing POCD outcomes for impairment on individual tests (z-scores < -1.96 below controls for that test), the highest frequencies were seen in the Trail Making Test B, the CERAD Auditory Verbal Learning Test, and the Controlled Oral Word Learning Test (Table 4). Impairment was detected across the entire range of tests in patients with PAF and PeAF, reflecting a generalized deficit in multiple tests in these patients. Abnormalities in patients with SVT were seen in 3 of 8 tests. One patient with SVT had evidence of neurocognitive decline at day 90, a 67-year-old man with hypertension and diabetes who underwent ablation of a left anterolateral pathway. During the procedure, left atrial access time was 56 min, with 1.5 min of RFA time. Of the 30 control patients with AF, an abnormality in 1 test was seen in 2 patients only (Table 4).

Factors associated with POCD. The patient data at day 2 and day 90 were analyzed by univariable analysis to identify associations between the development of POCD and other variables. The variables included in the univariable analysis were age, IQ, diabetes mellitus, hypertension, intraprocedural ACT and direct current cardioversion, and left atrial access time. At day 2, every 1-min increase in left atrial access time was associated with POCD on univariable analysis (odds ratio [OR]: 1.01; 95% CI: 1.00 to 1.01; $p = 0.04$). At day 90, increasing left atrial access time was also significantly associated with POCD on univariable analysis (OR: 1.01; 95%

Table 4 Impaired Performance at 90 Days on Neuropsychological Tests

	Paroxysmal Atrial Fibrillation (n = 60)	Persistent Atrial Fibrillation (n = 30)	Supraventricular Tachycardia (n = 30)	Controls (n = 30)	p Value
Consortium to Establish a Registry for Alzheimer's Disease/ Auditory Verbal Learning Test	6 (10)	3 (10)	0 (0)	0 (0)	0.09
Trail Making Test Part A	4 (7)	3 (10)	0 (0)	1 (3)	0.3
Trail Making Test Part B	2 (3)	5 (17)	1 (3)	0 (0)	0.02
Digit Symbol Substitution Test	3 (5)	1 (3)	2 (7)	0 (0)	0.6
Controlled Oral Word Association Test	7 (12)	1 (3)	2 (7)	0 (0)	0.2
Consortium to Establish a Registry for Alzheimer's Disease, Fluency	1 (2)	2 (7)	0 (0)	1 (3)	0.4
Grooved Pegboard Test, Dominant Hand	3 (5)	1 (3)	0 (0)	0 (0)	0.4
Grooved Pegboard Test, Nondominant Hand	2 (3)	1 (3)	0 (0)	0 (0)	0.6

Values are n (%).

CI: 1.00 to 1.02; p = 0.03). There were no other significant associations between POCD at day 90 and other variables (age: OR 1.0, 95% CI 0.96 to 1.09; IQ: OR 1.0, 95% CI 0.96 to 1.07; diabetes: OR 0.2, 95% CI 0.03 to 0.79; hypertension: OR 0.5, 95% CI 0.18 to 1.6; mean ACT: OR 1.0, 95% CI 1.0 to 1.02; direct current cardioversion: OR 1.0, 95% CI 0.71 to 1.51).

Discussion

The major finding of this study was that persistent POCD (at day 90) occurred in 13% of patients after ablation of PAF and 20% after ablation of PeAF. POCD was not observed in any of the control patients with AF (no ablation procedure) during the same time frame and in just 1 patient who underwent SVT ablation. In this population, neither cardiovascular risk factors nor intraprocedural direct current cardioversion was associated with POCD. Increased left atrial access time was significantly associated with POCD on univariable analysis.

Cerebral complications of ablation for AF. The combined risk of stroke/transient ischemic attack with current procedural and anticoagulation practices in ablation for AF has been reported to be approximately 0.5% to 1.0% (1). However, it is increasingly recognized that silent cerebral embolic events may occur more frequently than overt stroke. MRI studies have shown an prevalence of approximately 7% to 14% of new, apparently asymptomatic cerebral lesions after ablation for AF using irrigated catheters (2,3,13–16). In the series by Gaita et al. (2), periprocedural symptomatic stroke occurred at a frequency of 0.4%. However, post-procedural cerebral MRI was positive for new embolic lesions in 14% of patients who underwent irrigated RFA. In an elegant study in canines, Haines et al. demonstrated that microbubbles and particulate matter are responsible for new hyperintense lesions on MRI and that these lesions correlate with anatomic lesions on histopathologic analysis (17). In a long-term follow-up study of 9 patients with new silent cerebral infarction post-ablation for AF, there was an attenuation of radiological lesions over time with no residual lesions or scar seen on repeat MRI after a 21-month follow-up (18). In a similar study, Deneke et al. demonstrated that 94% of asymptomatic lesions resolved at up to 1 year post-ablation, with larger (>10 mm) acute lesions producing chronic glial scars at long-term follow-up (19). The neurological impact of these emboli is unclear and is likely to be determined by their size, number, and anatomic region. The sequelae of silent cerebral infarction may include subtle neurocognitive impairment (14), which is in turn associated with an increased lifetime risk of cognitive impairment (20).

Etiology of POCD. The etiology of POCD is likely to be multifactorial. The surgical procedure, anesthetic, and patient susceptibility are all likely to influence the vulnerability to POCD (21,22). In the current study, we compared post-procedural cognitive function at day 2 and day 90 with cognitive function immediately before the ablation. We observed an overall prevalence of POCD at day 2 of 24% and at day 90 of 13%. The higher early prevalence may in part reflect the reversible effect of anesthesia (23) on cognitive function. In patients undergoing cardiac surgery, this effect is most pronounced at hospital discharge and has been reported to improve by the time of late testing after 6 weeks (20). Late improvement may also be related to time-dependent improvement in cognition after an initial event.

Late post-procedural cognitive impairment (day 90) is more likely to directly reflect any intraprocedural cerebral insult, including subclinical cerebral ischemia (24). In a randomized study of 100 patients undergoing cardiac surgery, Pugsley et al. (24) found that patients randomized to an arterial line filter had a significantly lower number of cerebral microembolic events and were significantly less likely to have POCD at 8-week follow-up.

Neurocognitive dysfunction after coronary artery bypass grafting may be the result of cerebral microembolism (24) primarily originating from disruption of aortic atherosclerotic lesions (25,26) as well as recirculated lipid matter from the pericardial aspirate (27) and air entering the bypass circuit (28). Damage to small cerebral vessels from lipogenous material has been found at autopsy in patients after bypass surgery (29). In addition, cerebral injury is believed to be exacerbated by the systemic inflammatory response and mediator release activated by cardiopulmonary bypass and ischemia/reperfusion injury (29,30).

We observed no instances of time-dependent (over 90 days) cognitive decline in a nonprocedural AF population. In contrast, the AF procedural groups had a significantly higher prevalence of late POCD (day 90), and the strongest association was with left atrial access time. Prolonged access to the systemic circulation with the potential for microembolism may play an important role in the development of POCD. In a study of post-AF ablation MRI lesions, Gaita et al. (2) found that cardioversion and a procedural ACT <250 s were the only factors associated with the development of new lesions on imaging. Interestingly, in an analysis of patients with PeAF undergoing cardioversion alone, no silent embolic lesions were detected (2). This raises the suggestion that the prothrombotic milieu induced by catheter ablation is an important factor in the thromboembolic risk associated with cardioversion during an AF ablation procedure. In our population with a uniformly targeted ACT of 300 to 350 s, there was no association between either ACT or the prevalence of cardioversion and the risk of POCD.

Interestingly, in our relatively low-risk population, we found that POCD occurs independently of conventional cardiovascular risk factors. Increasing age and poorer performance on the estimated intelligence test were not associated with an increased prevalence of POCD in this study. This may be due to the relative homogeneity of the study population with uniformly young age (mean: 56 ± 10 years), low prevalence of cardiovascular risk factors, and high estimated IQ scores assessed by the National Adult Reading

Test (mean: 115 ± 14). Different results may have been obtained if a broader spectrum of patients (older with higher $CHADS_2$ scores) had been studied. The reasons for this remain speculative, but other factors not routinely screened may play a role. Cerebral hemodynamics, platelet function (31), and systemic inflammation (32) have been shown to be abnormal in patients with AF, and variability in these parameters may affect cognitive reserve and susceptibility to POCD.

Intraprocedural hypotension may directly cause cerebral injury or may exacerbate cerebral injury due to microembolism (33). However, hemodynamic effects are unlikely to have played a major role in POCD in our population, because the majority of patients had normal left ventricular function and were normotensive throughout the procedure.

We observed only 1 patient in the SVT group with evidence of late cognitive dysfunction, a 67-year-old man who underwent trans-septal puncture for a left anterolateral pathway ablation. A combination of procedural (left atrial access) and patient-related factors (age, diabetes, and hypertension) may have contributed to the development of cognitive dysfunction post-procedure in this individual. This patient had abnormal results on only 2 of the 8 tests.

Prior studies of cognitive dysfunction after cardiac procedures. POCD has been most extensively studied in patients after coronary artery bypass grafting. POCD has been documented in approximately 53% of patients at hospital discharge, 36% at 6 weeks post-operatively, and 24% at 6 months post-operatively (20). Although there is attenuation in the prevalence of POCD in the short-intermediate period after cardiac surgery, POCD at hospital discharge was significantly associated with both the severity and prevalence of cognitive decline at 5 years (20).

In a prior small series, Schwarz et al. compared the results of neurocognitive testing of 23 patients with AF undergoing ablation with either RFA or cryoablation with those of healthy community-based volunteers (14). By comparison, the patients with AF as a group had reduced scores on verbal memory post-ablation. Overall, 56.5% of patients who underwent ablation deteriorated from baseline on the verbal memory tests, which comprised 1 of 5 cognitive domains tested, compared with 17% of controls.

Clinical implications. This study demonstrates that ablation for AF may be associated with subtle neurocognitive impairment that persists at 90 days after the procedure. Further studies are required to determine whether these subtle abnormalities will be associated with an increased lifetime risk of cognitive impairment. Alternatively, cure of AF may in itself be protective in the longer term. The long-term cognitive implications will be an important determinant of procedural safety. Furthermore, strategies that reduce the left atrial access time, optimize the anticoagulation approach, and address the timing of direct current reversion may have an effect on the prevalence of POCD.

Study limitations. Many departments have recently adopted an approach of performing ablation for AF without interruption of warfarin therapy. Although this may potentially reduce the prevalence of POCD, a recent study showed an prevalence of clinical embolism of 0.6% (similar to that reported in earlier studies) despite a therapeutic international normalized ratio and ACT >300 s (34).

We did not perform diffusion-weighted MRI pre-ablation and post-ablation; therefore, correlation of neurocognitive outcomes with silent cerebral emboli could not be performed.

All procedures were performed under general anesthesia, and these results may not necessarily be applicable to patients who undergo the procedure under conscious sedation. Nevertheless, POCD persisted well beyond the time when the effects of anesthesia may continue to affect cognitive function.

Conclusions

Ablation for AF is associated with a 13% to 20% prevalence of POCD in patients with AF at long-term follow-up. These results were seen in a patient population with predominant $CHADS_2$ scores of 0 to 1, representing the majority of patients undergoing ablation for AF. The long-term implications of these subtle changes require further study.

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